

REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 6-8 under 35 U.S.C. § 112 (first paragraph) for indefiniteness is respectfully traversed in view of the above amendments.

Support for the claim amendments is found in the application as filed. The specification fully discloses that HCMV infection decreases the abundance of p21^{cip1} (page 26, line 29- page 28, line 12) and that the calpain inhibitors of the present invention protect p21^{cip1} degradation during HCMV infection (page 30, line 9- page 34, line 12). In addition, the application shows that calpain is activated by HCMV infection (page 35, line 1- page 36, line 31) and that calpain cleaves p21^{cip1} (page 37, line 1- page 38, line 20). The specification discloses that the calpain inhibitors of the present invention inhibit the proteolysis of p21^{cip1} (page 37, lines 21-22; Figure 19) and that a decrease in the level of p21^{cip1} is necessary for activation of E kinase activity and that activation of E kinase appears to be critical for efficient HCMV replication (page 3, lines 24-33).

The rejection of claims 6-7 and 14-15 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,015,787 to Potter et al. ("Potter") is respectfully traversed.

Potter relates to a fusion protein which includes a first portion that is capable of delivering the fusion protein into the cell and a second portion which includes a calpastatin peptide. In addition, Potter discloses that the fusion protein "may be used to inhibit activation of NF-KB regulated viruses, e.g. cytomegaloviruses . . .". Potter does not disclose or suggest a method of decreasing viral replication of a cytomegalovirus with a calpain inhibitor where the calpain inhibitor increases the levels of p21^{cip1}.

In contrast, as claimed in the present claims, the calpain inhibitor increases the levels of p21^{cip1}. There is no teaching or suggestion that the calpain inhibitors of Potter result in the increase of p21^{cip1}. In fact, Potter merely presents a hypothesis that the fusion protein will inhibit the activation of NF-KB regulated viruses. Potter is silent as to what affect, if any, the calpain inhibitor will have in the viral replication process. Thus, because Potter does not teach or suggest the cited claim limitation, the rejection is improper (See Manual of Patent Examining Procedure ("MPEP") 2131 ("To anticipate a claim, the reference must teach every element of the claim.")).

Further, Potter is not available as a reference against the claims of the present application. Potter does not contain an enabling disclosure for using a calpain inhibitor to decrease viral replication of a human cytomegalovirus (The stated test is whether a reference contains an enabling disclosure. See MPEP 2121.01). Potter provides no means to make and/or use a calpain inhibitor which is not a fusion protein. Further, Potter does not provide any information, other than the throwaway statement that the fusion protein may be used to inhibit activation of NF-KB regulated viruses, of how to make and/or use a calpain inhibitor which decreases viral replication where the calpain inhibitor increases p21^{cip1}. Accordingly, because Potter does not contain an enabling disclosure, it cannot be used as a prior art reference against the claims of the present application.

For all of the above reasons, the rejection of claims 6-7 and 14-15 as anticipated by Potter is improper and should be withdrawn.

The rejection of claims 6-8 and 14-16 under 35 U.S.C §103 as obvious over U.S. Patent No. 5,478,727 to Roizman et al. ("Roizman"), U.S. Patent No. 5,607,831 to Henkart et al.

("Henkart"), Kido et al., *Advances in Enzyme Regulation*, 36:325-347 (1996) ("Kido") and de Jong et al., *Antiviral Research*, 39:141-162 (1998) ("de Jong") is respectfully traversed.

Roizman relates to the identification and purification of a herpes protease. Roizman solely discloses **viral** proteases; Roizman does not, however, relate to decreasing levels of functional **cellular** protease in cells. Further, Roizman does not teach or suggest calpain inhibitors.

Henkart relates to calpain inhibitors and their use in preventing the progression of cell death, especially in individuals with HIV. Again, Henkart, like Roizman, do not relate to decreasing levels of functional **cellular** protease in cells. Further, Henkart does not relate to HCMV, but exclusively discloses HIV.

Kido relates to the cellular proteases involved in the pathogenicity of enveloped animal viruses, HIV, influenza virus A and Sendai virus. Kido does not relate to calpain inhibitors, nor does Kido relate to human cytomegalovirus.

de Jong relates to human cytomegalovirus and its persistence in latent form. de Jong further discloses CMV disease in HIV-infected persons being caused by reactivation of latent virus. de Jong, does not relate to calpain inhibitors or to methods of decreasing viral replication of a human cytomegalovirus.

Firstly, Roizman, Henkart, Kido and de Jong are not properly combinable. One skilled in the art of Roizman, which relates to identification of a herpes protease, would have no reason to look at Henkart, Kido or de Jong for answers. Likewise, one skilled in the various arts of Henkart (calpain inhibitor in treatment for HIV), Kido (activation of animal enveloped viruses) and de Jong (latent HCMV virus associated with HIV) would not have been motivated to look at the other

art for answers. It appears to be the reasoning of the U.S. Patent and Trademark Office ("PTO") that one skilled in the art would have been motivated to combine the references because de Jong teaches individuals with HIV infection also have HCMV infection. However, the PTO has provided no basis as to why one skilled in the art would have looked to any of the other references for a calpain inhibitor to treat HCMV infection. The references only disclose calpain inhibitors for treating HIV infection. NONE of the references teach or suggest use of a calpain inhibitor to treat HCMV. There is no motivation in any of the references, or in the state of the art, to suggest to one skilled in the art to use the calpain inhibitors of Henkart to treat anything other than HIV. Further, none of the references, nor the combination of references, suggest using calpain inhibitors to treat viral replication of HCMV by decreasing levels of a cellular protease. It appears to be the PTO's position that Kido provides this motivation, but Kido does not relate to HCMV. Thus, because there is no suggestion or motivation in the references themselves, or in the state of the art, to modify or combine the references, the rejection based on the combination is improper and must be withdrawn (See MPEP 2145(X)©)).

In addition, The PTO seems to be employing an impermissible "obvious to try" standard and the combination further appears to be based on impermissible hindsight (See MPEP (X)(A)-(B)). Prior to the present invention, there was no suggestion, either in the references, or in the state of the art, to treat viral replication of a HCMV with a calpain inhibitor. As discussed above, the cited references do not provide such motivation. One skilled in the art, having reviewed the cited references, would not have been motivated to use calpain inhibitors generally, nor the specifically identified calpain inhibitors of claims 8 and 16, because

there is not suggestion in de Jong, Kido or Roizman to modify Henkart to treat HCMV. As discussed above, Henkart relates to the treatment of HIV. Roizman relates to treatment of herpes viruses, via viral proteases. Therefore, any suggestion Roizman provides would be for modifying Henkart to treat viral replication by decreasing viral proteases, not cellular proteases as claimed in the present application. This deficiency is not overcome by de Jong, which merely recognizes the association of HIV with latent HCMV. Neither is this deficiency overcome by Kido, which discusses cellular proteases. Firstly, Kido does not suggest that decreasing levels of cellular proteases by any means, let alone calpain inhibitors generally or the specified calpain inhibitors, may be useful in the treatment of the viruses disclosed in Kido. Secondly, Kido, which does not disclose or suggest HCMV at all, does not suggest that decreasing levels of cellular proteases will be useful in decreasing viral replication of HCMV.

Further, even assuming that the combination of references is proper, which it is not, the cited combination does not teach or suggest a method of decreasing viral replication of a human cytomegalovirus where the calpain inhibitor increases the levels of p21^{cip1}.

For all of the above reasons, the rejections of claims 6-8 and 14-16 under 35 U.S.C §103 as obvious over the cited references is improper and must be withdrawn.

The rejection of claims 8 and 16 under 35 U.S.C. § 103 as obvious over Henkart and de Jong in view of Potter is respectfully traversed.

As discussed above in detail, Henkart and de Jong are not properly combinable. Further, Henkart and de Jong do not teach or suggest a method of decreasing viral replication of a human cytomegalovirus where the calpain inhibitor increases the levels of p21^{cip1}. Potter does not overcome these

deficiencies. Further, neither Henkart or de Jong suggest modifying Potter to utilize the particular calpain inhibitors as specified in claims 8 and 16, because Potter teaches that a fusion protein must be used to have a portion which will enter the cell. There is no suggestion in any of the references that Potter could be modified to use a calpain inhibitor alone (i.e. not a fusion protein).

In view of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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